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Trends in the incidence of ocular melanoma in the United States, 1974–1998

Peter D. Inskip*, Susan S. Devesa & Joseph F. Fraumeni, Jr.
Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA

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Abstract

Background: A recent report noted a fourfold risk of ocular melanoma associated with employment in occupations involving use of cellular telephones. *Methods*: To aid interpretation of this finding, and clarify how subsite-specific temporal variation in incidence of ocular melanoma compares with that for cutaneous melanoma, we examined time trends in the incidence of melanoma among whites in the United States, based on data collected through the surveillance, Epidemiology, and End Results (SEER) program for 1974–1998. *Results*: The incidence of ocular melanoma decreased over time in both sexes, with no indication of a recent increase during the 1990s. The annual percent change was −0.7% for males (95% confidence interval: −2.3, 0.9) and −1.2% for females (95% confidence interval: −2.5, 0.0). Time trends appeared to differ by subsite of ocular melanoma; rates were flat for the choroid, decreased for the ciliary body, and increased for the conjunctiva (among males only) beginning in the 1980s. In contrast, all subsites of cutaneous melanoma, including the face and adjacent areas, showed marked increases in incidence over the observation period. *Conclusions*: The dramatic increase in use of cellular telephones has not been accompanied by an increase in the incidence of ocular melanoma. Further study is required to explain the different time trends for subsites of ocular melanoma, and for ocular *versus* facial and other cutaneous melanomas.

Introduction

Ocular melanoma is the most common type of eye cancer among adults and is often fatal or results in loss of vision in the affected eye [1, 2]. The etiology is largely unknown [1–14]. Some studies indicate the role of sunlight or artificial sources of exposure to ultraviolet radiation (UVR) [3–12], but the evidence is mixed [1, 13, 14]. Only a small percentage of UVR incident to the eye actually reaches the choroid, where most ocular melanomas arise [15]. Other evidence suggests the influence of genetic susceptibility or other host factors [1, 2, 5–7, 16]. The extent to which ocular melanoma shares risk factors with cutaneous melanoma is unclear. In this paper, we examine time trends in the incidence of ocular melanoma in the United States for the period 1974–1998 and contrast these trends with those for facial and other cutaneous melanoma. Whether there has been a recent increase in the incidence of ocular melanoma is of particular interest in light of a recent report indicating a fourfold risk of ocular melanoma associated with employment in jobs judged likely to involve exposure to radiofrequency (RF) radiation from cellular telephones [17, 18].

Materials and methods

The analysis is based on the US cancer incidence data for 1974–1998 that were collected through the Surveillance, Epidemiology, and End Results (SEER) program [19]. The original nine population-based cancer registries included in the SEER program include the states of Connecticut, Hawaii, Iowa, New Mexico and Utah, plus the metropolitan areas of Atlanta (Georgia), Detroit (Michigan), San Francisco (California) and Seattle (Washington). Together, these cover approximately 10% of the US population. With the addition of Los

* Address correspondence to: Peter D. Inskip, Radiation Epidemiology Branch, National Cancer Institute, Executive Plaza South, Room 7052, 6120 Executive Blvd.; Bethesda, MD 20892-7238, USA. E-mail: inskippe@mail.nih.gov

Angeles and expansion of the San Francisco reporting area in 1992, SEER coverage increased to about 14% of the US population. We describe trends for the original and expanded reporting areas separately. Trends are shown for all whites for the nine SEER areas (1974–1998) and for non-Hispanic whites for the years 1992–1998. Separate rates for Hispanic and non-Hispanic whites were not available for the entire time period. We included malignant melanomas (ICD-O-2 histology code 8720-8774; behavior = 3) of the eye or orbit (sites: 690–699) [20]. For comparison, we also considered trends in the incidence of cutaneous melanoma of the face and ear (sites: 440–443), scalp and neck (site: 444), and trunk and limbs (sites: 445–447). Age-specific and age-adjusted rates, directly standardized to the 1970 US population, were calculated and expressed per 100,000 person-years. Loglinear models were used to estimate the annual percent change in incidence rates and calculate 95% confidence intervals (CIs). Regressions were weighted inversely in proportion to variance, by the number of cases occurring in each year. Trend analyses were repeated using three alternative standard populations (world, 1940 US and 2000 US).

Results

During the period 1974–1998, 3202 ocular melanomas were reported to the nine SEER registries (3110 among whites). These included 2012 tumors of the choroid, 527 of the ciliary body, 167 of the conjunctiva, and 496 of other, multiple, or unspecified sites. The category 'ciliary body' also includes tumors for which the site was described as iris, lens, sclera, uveal tract, intraocular or eyeball. There were 1528 tumors reported in the right eye and 1569 in the left eye; laterality was unspecified for 105 tumors.

The proportion of microscopically confirmed tumors varied by subsite: 80% for choroid, 86% for ciliary body, 99% for conjunctiva, and 82% overall. For choroidal melanomas, there was a decrease in the proportion with microscopic confirmation over time, from 95% in 1974–1979, to 81% for 1980–1989, to 71% for 1990–1998. The corresponding confirmation rates for ciliary body tumors were 95%, 83% and 82%, respectively. Confirmation rates were uniformly high over this time period for conjunctival melanoma.

The incidence rate was decidedly higher for whites than for blacks and for non-Hispanic whites than for Hispanic whites. The incidence rate for 1974–1998 among all whites was 0.69 per 100,000 person-years among males and 0.54 among females. Corresponding rates among blacks were 0.08 per 100,000 for males and 0.03 for females. Only 12 cases of ocular melanoma occurred among blacks during 1992–1998, too few to detect a possible trend, so trend analyses focused on whites. For the years 1992–1998, the incidence rate among white Hispanics was 0.15 per 100,000 among males and 0.21 per 100,000 among females. Among non-Hispanic whites, the rates were 0.71 and 0.52 per 100,000 in males and females, respectively.

There was no indication of an increasing trend in incidence over time among whites for either sex (Table 1; Figure 1). The incidence rate appears to have remained flat or decreased over the observation period as a whole, with no upturn during the 1990s. The annual percent change was −0.7% for males (95% CI: −2.3, 0.9) and −1.2% for females (95% CI: −2.5, 0.0). These results were insensitive to the choice of standard population. Narrowing the time window to 1992–1998 and restricting analysis to non-Hispanic whites (Table 1; Figure 1), or stratifying by age at diagnosis (Table 2), failed to reveal any sign of a recent increase in incidence. Trends were flat or decreasing for the combined registries of Los Angeles, San Francisco and San Jose, California, regions where widespread cell phone use might have occurred sooner than in other SEER areas (data not shown).

The eye on the side of the head on which a cellular phone is used would be more highly exposed to RF radiation than the eye on the contralateral side. In a recent case–control study of brain tumors and cellular telephone use among the US adults [21], study participants were asked which hand they generally used to hold the phone. Among controls, 58% reported typically using their right hand, 34% typically using their left hand, and 8% using either or both hands. These percentages are similar to those reported elsewhere [22]. If these data are broadly representative of the US population, and if cellular telephone use causes ocular melanoma, one would expect to see a recent trend towards a higher proportion of right-sided tumors. No such trend in tumor laterality was seen for either sex (Table 3). Among males, there was a decrease in the incidence of right-sided tumors and little change in the rate of left-sided tumors. Among females, decreases in the incidence of ocular melanoma were observed on both sides. Over the entire time period, the ratio of right- to left-sided tumors was 1.00 for females and 0.97 for males.

Time trends in incidence differed by subsite of ocular melanoma (Table 4). There was no clear trend for melanoma of the choroid, the most common location. The incidence of conjunctival melanoma, an uncommon site, increased among males starting in the mid-1980s, but not females. The increase was not confined to any

Table 1. Number of malignant ocular melanoma cases and incidence rates among whites for SEER reporting areas, by sex and year of diagnosis

Year of diagnosis	Males		Females		Both sexes	
	Cases	Rate[a]	Cases	Rate[a]	Cases	Rate[a]
Nine SEER reporting areas, all whites						
1974–1998	1591	0.69	1519	0.54	3110	0.61
1974–1978	315	0.78	318	0.64	633	0.71
1979–1983	316	0.73	302	0.58	618	0.65
1984–1988	276	0.61	277	0.49	553	0.54
1989–1993	332	0.69	316	0.52	648	0.60
1994–1998	352	0.67	306	0.49	658	0.57
1994	66	0.65	61	0.47	127	0.55
1995	88	0.84	66	0.57	154	0.69
1996	59	0.56	60	0.49	119	0.52
1997	69	0.64	56	0.45	125	0.53
1998	70	0.64	63	0.49	133	0.56
Annual change[b], % (95% CI)	−0.7 (−2.3, 0.9)		−1.2 (−2.5, 0.0)		−1.0 (−2.5, 0.5)	
Eleven SEER reporting areas, non-Hispanic whites[c]						
1992–1998	621	0.71	543	0.52	1164	0.60
1992	79	0.67	75	0.49	154	0.57
1993	80	0.65	84	0.56	164	0.60
1994	95	0.76	76	0.49	171	0.61
1995	115	0.92	81	0.58	196	0.73
1996	74	0.58	77	0.52	151	0.55
1997	98	0.75	71	0.47	169	0.60
1998	80	0.61	79	0.51	159	0.55
Annual change, % (95% CI):	−0.8 (−9.3, 8.5)		−0.7 (−4.6, 3.3)		−0.8 (−6.0, 4.8)	

[a] Per 100,000 per year (age-adjusted, 1970 US standard).
[b] Based on 5-year groupings, 1974–1978 through 1994–1998.
[c] Two new SEER reporting areas were added in 1992 (see text).

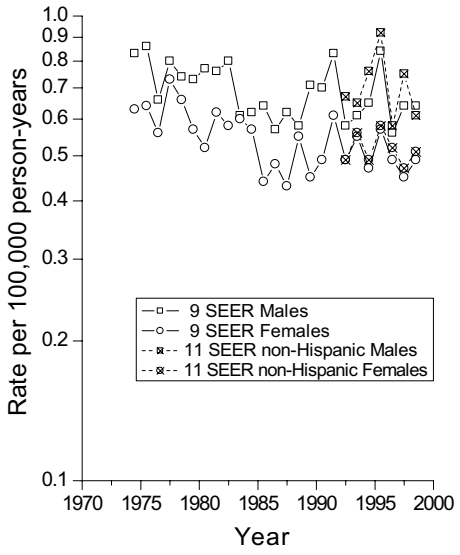

Fig. 1. Trends in incidence of malignant ocular melanoma among whites, by sex, during 1974–1998 (nine SEER areas) and 1992–1998 (11 SEER areas). The 1974–1998 rates are for all whites, whereas the 1992–1998 rates are for non-Hispanic whites. Rates are age-adjusted (1970 US standard) and plotted on a log scale.

single registry. In both sexes, the overall decreasing trend for ocular melanoma was due to declining rates for tumors coded to ciliary body and to other or unspecified locations.

Whereas the incidence of ocular melanoma appeared to decrease since the early 1970s, the incidence of cutaneous melanoma rose considerably over the same period (Table 5). Similar increases were reported for cutaneous melanoma of the face and ears, the scalp and neck, and the trunk and limbs, with the trends more pronounced among males than females.

Discussion

In the United States, the incidence of ocular melanoma has remained flat or declined since 1974, with no evidence of an upturn in the 1990s that might be anticipated on the basis of a reported excess risk associated with cellular phone use in Germany [17]. This was the case both overall, and within subgroups defined by age, sex and geography that might be expected to have a higher proportion of longer-term

Table 2. Number of malignant ocular melanoma cases and incidence rates among non-Hispanic whites for 11 SEER reporting areas (1992–1998), by sex, age and year of diagnosis

Sex	Age (years)	Year of diagnosis				Rate ratio[b]	95% CI
		1992–1995		1996–1998			
		Cases	Rate[a]	Cases	Rate[a]		
Males	0–49	81	0.19	53	0.15	0.79	0.56–1.12
	50–64	111	1.82	74	1.53	0.84	0.63–1.13
	≥65	177	3.44	125	3.16	0.92	0.73–1.15
Females	0–49	77	0.18	49	0.16	0.89	0.62–1.27
	50–64	75	1.18	56	1.13	0.96	0.68–1.35
	≥65	164	2.25	122	2.20	0.98	0.77–1.24

[a] Per 100,000 year (age-adjusted, 1970 US standard).
[b] Rate for 1996–1998/rate for 1992–1995 (age-adjusted).

Table 3. Incidence rates of ocular melanoma among whites by sex, tumor laterality, and year of diagnosis (based on nine SEER reporting areas), 1974–1998

Year of diagnosis	Incidence rate[a,b]					
	Males			Females		
	Right	Left	Right:left	Right	Left	Right:left
1974–1978	0.42	0.33	1.27	0.29	0.34	0.85
1979–1983	0.35	0.38	0.92	0.28	0.29	0.97
1984–1988	0.29	0.29	1.00	0.24	0.22	1.09
1989–1993	0.31	0.34	0.91	0.25	0.24	1.04
1994–1998	0.28	0.38	0.74	0.24	0.24	1.00
All years	0.33	0.34	0.97	0.26	0.26	1.00

[a] Tumors not specified as to one side or the other are excluded. Thus, the rates do not sum to the rates in Table 1.
[b] Per 100,000 per year (age-adjusted, 1970 US standard).

users of cellular phones [21]. It would be surprising for cell phone use to be associated with a several-fold increased risk of ocular melanoma, but show no effect on the US population rates through 1998. Recent estimates place the number of cellular telephone subscribers in the US at more than 137 million [23], which represents a more than thousand-fold increase since 1984. Widespread use of cellular phones occurred somewhat later in the US than in Europe or Asia [24], and we cannot rule out the possibility that it is too early to detect a resultant increase in incidence; however, the time difference was not dramatic, and a recent analysis of trends in the incidence of ocular melanoma in Denmark through 1996 also failed to reveal an upturn [25].

Although not significantly different from zero, the slope of the time trend in ocular melanoma incidence for 1974–1998 was negative. Improvements in diagnostic precision or changes in diagnostic methods might have contributed to a long-term, downward trend. While the diagnosis of ocular melanomas has been highly accurate over the past decade, some benign ocular tumors or other lesions (*e.g.*, nevi) may have been incorrectly diagnosed as melanoma in earlier years [26–28]. Second, the proportion of melanomas of the choroid and ciliary body that were microscopically confirmed decreased with time. Lesions in the posterior uvea are less accessible to biopsy than are those in the anterior eye [29] and, historically, microscopic diagnoses may have been more likely to be based on surgical than biopsy specimens. There have been major advances in the ability to diagnose posterior tumors by non-invasive means, and some clinically diagnosed patients are not treated surgically, as there is disagreement about whether optimal therapy includes enucleation [29]. If SEER historically underascertained clinically diagnosed ocular melanomas, as was found to be the case in Israel [30], there could be a downward bias in estimated time trends. However, most of the decrease in the rate of microscopic confirmation had occurred by the early

Table 4. Number of ocular melanoma cases and incidence rates among whites for nine SEER reporting areas, by location within the eye, sex and year of diagnosis, 1974–1998

Sex	Year of diagnosis	Choroid[a]		Ciliary body[a]		Conjunctiva[a]		Other and unspecified[a]	
		Cases	Rate[b]	Cases	Rate[b]	Cases	Rate[b]	Cases	Rate[b]
Male	1974–1978	173	0.42	75	0.19	4	0.01	63	0.15
	1979–1983	231	0.53	38	0.09	13	0.03	34	0.08
	1984–1988	158	0.35	62	0.13	17	0.04	39	0.09
	1989–1993	208	0.43	48	0.10	25	0.05	51	0.11
	1994–1998	252	0.48	36	0.07	28	0.05	36	0.07
Annual change[c], % (95% CI)		0.0 (−3.4, 3.6)		−4.0 (−9.2, 1.5)		5.5 (−0.6, 12)		−2.9 (−7.6, 2.1)	
Female	1974–1978	173	0.35	63	0.13	14	0.03	68	0.13
	1979–1983	196	0.37	48	0.09	15	0.03	43	0.08
	1984–1988	157	0.28	60	0.10	9	0.01	51	0.09
	1989–1993	202	0.33	50	0.08	12	0.02	52	0.09
	1994–1998	216	0.35	36	0.06	16	0.02	38	0.06
Annual change[c], % (95% CI)		−0.2 (−2.4, 2.1)		−3.2 (−5.6, −0.7)		−1.2 (−7.2, 5.1)		−3.4 (−6.7, 0.1)	

[a] ICD-O-2 topography categories are choroid (693), ciliary body (694), conjunctiva (690), and other and unspecified (691,692, 695–699). The category for ciliary body includes site specified as iris, lens, sclera, uveal tract, intraocular and eyeball.
[b] Per 100,000 per year (age-adjusted, 1970 US standard).
[c] Based on 5-year groupings, 1974–1978 through 1994–1998.

Table 5. Incidence rates for cutaneous melanoma of the face and ears, scalp and neck, and trunk and limbs, separately by sex and year of diagnosis (based on nine SEER reporting areas), 1974–1998

Year of diagnosis	Incidence rate[a]					
	Face and ears[b]		Scalp and neck[c]		Trunk and limbs[d]	
	Males	Females	Males	Females	Males	Females
1974–1978	1.33	0.76	0.62	0.31	5.69	5.95
1979–1983	1.63	0.84	0.79	0.43	7.99	7.86
1984–1988	2.31	0.90	1.02	0.43	9.83	9.02
1989–1993	2.69	1.08	1.32	0.46	11.62	9.80
1994–1998	3.22	1.19	1.65	0.53	13.66	11.34
Annual change[e], %	4.5 (3.2, 5.8)	2.4 (1.7, 3.1)	5.0 (4.8, 5.3)	2.2 (0.6, 3.8)	4.1 (2.9, 5.4)	2.9 (1.8, 4.1)

[a] Per 100,000 per year (age-adjusted, 1970 US standard).
[b] Includes lip, eyelids, external ear, and other face, not otherwise specified (ICD-O-2 sites 440-443).
[c] Site 444.
[d] Sites 445–447.
[e] Based on 5-year groupings, 1974–1978 through 1994–1998.

1990s, so such an effect would not obscure a recent, real increase in incidence. In more recent years, needle biopsy of lesions in the back of the eye has come to be regarded as a safe and reliable diagnostic tool, except for small lesions [31]. Thus, changes in accuracy or method of diagnosis are more of an issue for long-term trends in incidence than for changes over the past decade.

Another factor contributing to a declining trend in the white population over the 25-year period may be the increasing population of Hispanics, who have much lower rates of ocular melanoma. We were able to separate Hispanic and non-Hispanic whites for 1992–1998, so it is unlikely that a cell phone effect was obscured by population admixture.

Exposure to solar radiation is an established risk factor for cutaneous melanoma and may be involved in ocular melanoma [2–12]. However, the incidence rates for ocular melanoma were relatively stable in western

countries from the 1940s through the early 1980s, while the rates for cutaneous melanoma increased sharply [30, 32–34]. A survey in Denmark revealed that the increases in facial melanoma were less pronounced than for melanoma of the trunk and limbs [32]. Our study updates earlier reports by showing that the rates for ocular melanoma in the US have declined or remained flat over the past quarter century, while the relative increase of facial melanoma resembles that of other cutaneous melanomas. The increase in sunlight-related melanomas of the face, but not the eye, might be attributed to the shielding of interior structures of the eye by the cornea and lens, possibly coupled with the increasing use of sunglasses [15, 32]. It is also possible that the relative importance of occupational *versus* recreational exposure to solar radiation differs between ocular and cutaneous melanoma. Alternatively, genetic or other host factors may play a greater etiologic role than solar radiation for the more common types of ocular melanoma [1, 14, 16].

The only subsite of ocular melanoma with an increasing trend in our study was the conjunctiva, the part of the eye most highly exposed to UV radiation. However, this trend was seen in males only and was of borderline significance. The geographic correlation between conjunctival melanoma and sunlight exposure in the US is weak [35]. Increased incidence of conjunctival squamous cell carcinoma, but not melanoma, has been reported in association with HIV infection [36, 37]. In the present study, the increase did not appear to be concentrated in HIV-endemic areas. Parts of the cornea, iris, sclera and ciliary body are also exposed to UV radiation, but the incidence of melanoma at these subsites collectively decreased over time. The reasons for the downward time trends are unclear, particularly since facial melanomas are increasing. An artifact related to changes in clinical practice cannot be excluded. Our findings indicate the need for further studies into risk factors that may explain the different time trends for subsites of ocular melanoma, and for ocular *versus* facial and other cutaneous melanomas. In addition, results provide no support for the hypothesis that use of cellular telephones causes ocular melanoma.

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